Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/13/2020
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Gamma Globin (HBG1 and HBG2) Sequencing

ARUP test code 3001957

Specimen HBG FGS	Whole Blood
HBG FGS Interpretation	See Note *

Corrected

This is a corrected report.

Originally reported on 6/19/2020 as no pathogenic variants were detected in the HBG1 and HBG2 genes. This report has been updated to include the benign XmnI variant that was detected in the HBG2 gene.

TEST PERFORMED - 3001957
TEST DESCRIPTION - Gamma Globin (HBG1 and HBG2) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
No pathogenic variants were detected in the HBG1 and HBG2 genes. One copy of the benign XmnI variant was detected in the HBG2 gene.

INTERPRETATION
No pathogenic variants were detected in the HBG1 or HBG2 genes using bidirectional sequencing of all coding regions, intron/exon boundaries, and proximal promoters. This result reduces the likelihood of a gamma globinopathy. One copy of the benign XmnI variant, HBG2 c.-211C>T, was detected by sequencing. By itself the Xmnl variant is considered clinically benign; however, this variant has been associated with higher levels of Hb F when it is inherited in combination with some beta globin (HBB) gene variants. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. If there is clinical suspicion of hereditary hemolytic anemia, consideration may be given to the Hereditary Hemolytic Anemia Panel Sequencing (ARUP test code 2012052). If suspicion for a hemoglobinopathy remains, consideration may be given to Hemoglobin Reflexive Cascade (ARUP test code 2005792).

BENIGN VARIANT
HBG2: c.-211C>T; Heterozygous
Commonly Known As: XmnI

The HBG2 c.-211C>T variant (rs7482144, rs1060499525), also known

H=High, L=Low, *=Abnormal, C=Critical

as -158C>T and XmnI, is a common variant in the 5' untranslated region. While not associated with hereditary persistence of fetal hemoglobin (HPFH) in healthy adults, this variant has been described as a modifier of beta-thalassemia (Ma 2007, Nguyen 2010) and beta-globin variants such as Hb S (Akinbami 2016) due to its association with increased levels of HbF. This variant is also reported in ClinVar (Variation ID: 14984) and is found in the general population with an overall allele frequency of 20.7% (at least 6412/30916 alleles) in the Genome Aggregation Database. Based on available information, this variant is considered to be benign.

COMMENTS
Reference Sequences: GenBank # NM_000559.2 (HBG1), NM_000184.2 (HBG2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
All other likely benign and benign variants are not reported.

REFERENCES
Akinbami AO et al. Hereditary Persistence of Fetal Hemoglobin Caused by Single Nucleotide Promoter Mutations in Sickle Cell Trait and Hb SC Disease. Hemoglobin. 2016;40(1):64-5. PMID: 26372199.

Ma Q et al. Beta-globin gene cluster polymorphisms are strongly associated with severity of HbE/beta(0)-thalassemia. Clin Genet. 2007 Dec;72(6):497-505. PMID: 17894837.

Nguyen TK et al. The XmnI (G)gamma polymorphism influences hemoglobin F synthesis contrary to BCL11A and HBS1L-MYB SNPs in a cohort of 57 beta-thalassemia intermedia patients. Blood Cells Mol Dis. 2010 Aug 15;45(2):124-7. PMID: 20472475.

This result has been reviewed and approved by

Corrected from Negative [NA] on 09/24/21 14:09:08 MDT by .

BACKGROUND INFORMATION: Gamma Globin (HBG1 and HBG2) Sequencing
CHARACTERISTICS: Variants in the gamma globin genes, HBG1 and HBG2, may occasionally result in either a quantitative defect (gamma thalassemia or nondeletional hereditary persistence of fetal hemoglobin) or a qualitative abnormality (gamma variant). Gamma variants resulting in unstable, high- and low-oxygen affinity or M hemoglobin variants may result in hemolytic anemia/hyperbilirubinemia, erythrocytosis/cyanosis, or methemoglobinemia in neonates, respectively. Clinical symptoms related to gamma globin variants commonly resolve after the first six months of life given the switch from fetal hemoglobin expression to adult hemoglobin expression.
INCIDENCE: Unknown.
INHERITANCE: Autosomal dominant.
CAUSE: Pathogenic germline variants in HBG1 or HBG2.
CLINICAL SENSITIVITY: Unknown. Gamma globin variants are a rare cause of neonatal hemolytic anemia, cyanosis, erythrocytosis, or methemoglobinemia.
METHODOLOGY: Long range PCR followed by nested PCR and bidirectional sequencing of all coding regions, intron-exon boundaries, and 5' proximal promoters of the HBG1 and HBG2 genes.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations or repeat element insertions. Large deletions/duplications, distal regulatory region variants, deep intronic variants, and hybrid gene events will not be detected.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or

approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Specimen HBG FGS	20-150-401588	5/29/2020 11:08:00 AM	5/29/2020 5:14:17 PM	6/19/2020 11:31:00 AM
HBG FGS Interpretation	20-150-401588	5/29/2020 11:08:00 AM	5/29/2020 5:14:17 PM	9/24/2021 2:09:00 PM

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical